PATENT APPLICATION

IN THE UNITED STATES PATENT
AND TRADEMARK OFFICE

Applicants:

Rodriguez et al.

Serial No.: 10/051662

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For: Prevention of Ovarian Cancer by Administering a Vitamin D Compound

Group Art Unit: 1614

Examiner: R. Cook

DECLARATION OF DR. GUSTAVO C. RODRIGUEZ UNDER 37 C.F.R. 1.132

1. I, Dr. Gustavo C. Rodriguez, am a co-inventor of the above application.

2. I am a graduate of the University of Illinois Medical School, having obtained the degree of Doctorate of Medicine (M.D.) in 1985. From 1985-1989, I received residency training in obstetrics and gynecology at the University of Illinois. From 1989-1992, I received specialty training in gynecologic oncology at Duke University. Since 1989, I have continuously engaged in research and development activities directly related to gynecological oncology, including ovarian cancer. I have conducted and directly supervised numerous research projects investigating gynecological oncology, including ovarian cancer. I have authored or co-authored over 50 articles and technical papers related to the field of gynecological oncology.

3. I am currently an Associate Professor at the Northwestern University Feinberg School of Medicine and Adjunct Associate Professor in the Department of Obstetrics and Gynecology at Duke University. I am the Director of the Division of Gynecologic Oncology at Evanston Northwestern Healthcare, where I supervise an ovarian cancer prevention research program and provide medical care to women with gynecological cancers, including both the surgical and chemotherapeutic management of women with cancers such as ovarian cancer.

4. The invention which is the subject of this application relates to a pharmacologic method to prevent ovarian cancer by administering to women a composition containing a progestin as well as Vitamin D. The basis of the invention is summarized in detail in the detailed description provided in the patent disclosure. Briefly, epidemiological evidence has shown that routine use of the combination estrogen–progestin oral contraceptive pill (OCP) confers a 30-50% reduction in the risk of developing subsequent epithelial ovarian cancer, suggesting that an effective ovarian cancer preventive approach using hormones is possible. Investigations by our group have elucidated a mechanism that we believe is responsible for the ovarian cancer preventive effects the OCP. Specifically, we have discovered that the progestin component of the OCP is functioning as a classic chemopreventive agent, by activating potent molecular pathways known to be associated with cancer prevention such as apoptosis in the ovarian surface epithelium. Our laboratory and animal research findings are supported by human data demonstrating that progestin-potent OCPs confer twice the ovarian cancer protection as newer weak-progestin OCPs. These human data provide proof of principle that progestins are effective chemopreventive agents for ovarian cancer, and suggest that a

regimen that has enhanced chemopreventive biologic potency in the ovarian epithelium will be more effective than a lower potency regimen for ovarian cancer prevention. This discovery is completely distinct from what has been previously presumed to be the mechanism underlying the protective effect of OCP use against ovarian cancer, namely that OCP use inhibits ovulation-induced genetic damage in the ovary.

5. The finding that apoptotic effects of progestins are a major biologic event underlying the ovarian cancer preventive effect of the OCP also opens the door toward both development of a more effective preventive than the currently formulated OCPs, as well as the discovery and development of other (non-progestin) agents that also selectively activate apoptosis in the ovarian epithelium as potential chemopreventive agents for ovarian cancer. Among the non-progestins, we have gathered important evidence in support of Vitamin D as a potent ovarian cancer preventive. This includes results from a prevention trial that we have performed in the chicken ovarian cancer animal model suggesting an additive ovarian cancer protective effect of Vitamin D when added to progestin, as well as studies that we have performed *in vitro* in cells derived from the human ovarian epithelium demonstrating that Vitamin D acts synergistically when combined with progestin, opening the door toward development of a very effective ovarian cancer preventive.

6. I have carefully read the Need reference, and conclude that the Need reference does not disclose any data that would motivate a physician or any scientist to use or develop a pharmacologic composition comprised of a progestin and Vitamin D for any purpose. In fact, the data presented by Need would argue against administering a regimen combining Vitamin D and progestin. The Need study sought to

determine the impact of the combination of a progestin and Vitamin D for the prevention of osteoporosis. The data presented show no significant enhancement in bone mineral density in women on calcium who received progestin plus Vitamin D as compared to those who received progestin alone. In fact, the addition of Vitamin D appeared to somewhat abrogate the beneficial effect of the progestin (+ 4.4 mg/ml/yr forearm mineral density in women on progestin plus calcium, versus a lower bone density of +3.9 mg/ml/year forearm mineral density in women who received progestin plus calcium PLUS Vitamin D). Thus, Need teaches away from the use of Vitamin D in combination with a progestin. Given the data and teaching of Need, a reasonable physician or other scientist or practitioner would elect to not administer the progestin/Vitamin D combination, since the maximal effect would be achieved with progestin alone, and thus there would be no need to add the Vitamin D compound with its potential side effects without any commensurate benefit to the patient.

7. Additionally, I note that Need does not teach the higher dosages of Vitamin D that are part of my invention, nor does Need provide any motivation at all to use higher Vitamin D dosages. As I previously noted, if anything, Need's use of Vitamin D appeared to somewhat abrogate the beneficial effect of the progestin.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statement were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 9/1/04

Gustavo C. Rodriguez